



AETNA BETTER HEALTH®  
Coverage Policy/Guideline

Name:	Growth Hormones: Norditropin, Genotropin, Humatrope, Nutropin AQ, Omnitrope, Saizen, Zomacton	Page:	1 of 10
Effective Date:	6/9/2025	Last Review Date:	5/15/2025
Applies to:	<input checked="" type="checkbox"/> Florida Kids		

**Intent:**

The intent of this policy/guideline is to provide information to the prescribing practitioner outlining the coverage criteria for the Growth Hormone class that includes Norditropin, Genotropin, Humatrope, Nutropin AQ, Omnitrope, Saizen, and Zomacton under the patient's prescription drug benefit.

**Description:**

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, and the member has no contraindications or exclusions to the prescribed therapy.

**A. FDA-Approved Indications**

1. Pediatric patients with growth failure due to any of the following:
  - a. Growth hormone (GH) deficiency
  - b. Turner syndrome
  - c. Noonan syndrome
  - d. Small for gestational age (SGA)
  - e. Prader-Willi syndrome
  - f. Chronic kidney disease (CKD)
  - g. Short stature homeobox-containing gene (SHOX) deficiency
2. Adults with childhood-onset or adult-onset GH deficiency

**B. Compendial Uses**

1. Growth failure associated with any of the following:
  - a. Cerebral palsy
  - b. Congenital adrenal hyperplasia
  - c. Cystic fibrosis
  - d. Russell-Silver syndrome

All other indications are considered experimental/investigational and not medically necessary.

**Applicable Drug List:**

**Preferred Agent:**

Humatrope  
Norditropin

**Non-Preferred Agents:**

Genotropin  
Nutropin AQ  
Omnitrope  
Saizen



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Zomacton

### Policy/Guideline:

#### FORMULARY PREFERENCING

The patient is unable to take Humatrope and Norditropin, the preferred formulary alternatives, for the given diagnosis due to a trial and inadequate treatment response or intolerance, or a contraindication.

## I. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review (where applicable):

Both initial and continuation of therapy requests:

- Growth chart
- Pretreatment or current insulin-like growth factor-1 (IGF-1) level (laboratory report or medical record documentation)

Initial requests:

- Support for the diagnosis of neonatal GH deficiency (medical documentation, laboratory report, or imaging report)
- Pretreatment growth hormone provocative test result(s) (laboratory report or medical record documentation)
- Laboratory test reports of the following:
  - Diagnostic karyotype results in Turner syndrome
  - Diagnostic genetic test results in Prader-Willi syndrome
  - Diagnostic molecular or genetic test results in SHOX deficiency

Continuation of therapy requests:

- Total duration of treatment (approximate duration is acceptable)
- Date of last dose administered
- Approving health plan/pharmacy benefit manager
- Date of prior authorization/approval
- Prior authorization approval letter

IGF-1 levels vary based on the laboratory performing the analysis. Laboratory-specific values must be provided to determine whether the value is within the normal range.

## II. CRITERIA FOR INITIAL APPROVAL

### A. Pediatric Growth Hormone (GH) Deficiency

Authorization of 6 months may be granted to members with pediatric growth hormone (GH) deficiency when EITHER of the following criteria is met:



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- Member is a neonate or has a diagnosis of GH deficiency as a neonate (e.g., hypoglycemia with random GH level, evidence of multiple pituitary hormone deficiency, magnetic resonance imaging [MRI] results).
- Member meets ALL of the following criteria:
  - Member has EITHER of the following:
    - Two pretreatment pharmacologic provocative GH tests with both results demonstrating a peak GH level <10 ng/mL
    - A documented pituitary or central nervous system (CNS) disorder (see Appendix A) and a pretreatment IGF-1 level >2 standard deviations (SD) below the mean
  - For members < 2.5 years of age at initiation of treatment, the pretreatment height is >2 SD below the mean and growth velocity is slow
  - For members ≥ 2.5 years of age at initiation of treatment, member has either of the following:
    - Pretreatment height is >2 SD below the mean and 1-year height velocity is >1 SD below the mean
    - Pretreatment 1-year height velocity is >2 SD below the mean
  - Epiphyses are open

**B. Small for Gestational Age (SGA)**

Authorization of 6 months may be granted to members born small for gestational age (SGA) when ALL the following criteria are met:

- Member meets at least ONE of the following:
  - Birth weight < 2500 g at gestational age > 37 weeks
  - Birth weight or length less than 3rd percentile for gestational age
  - Birth weight or length ≥ 2 SD below the mean for gestational age
- Pretreatment age is ≥ 2 years
- Member failed to manifest catch-up growth by age 2 (i.e., pretreatment height >2 SD below the mean)
- Epiphyses are open

**C. Turner Syndrome**

Authorization of 6 months may be granted to members with Turner syndrome when ALL the following criteria are met:

- Diagnosis was confirmed by karyotyping
- Pretreatment height is less than the 5<sup>th</sup> percentile for age
- Epiphyses are open

**D. Growth Failure Associated with Chronic Kidney Disease (CKD), Cerebral Palsy, Congenital Adrenal Hyperplasia, Cystic Fibrosis, or Russell-Silver Syndrome**



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Authorization of 6 months may be granted to members with chronic kidney disease (CKD), cerebral palsy, congenital adrenal hyperplasia, cystic fibrosis, or Russell-Silver syndrome when ALL the following criteria are met:

- For members < 2.5 years of age at initiation of treatment, the pretreatment height is > 2 SD below the mean and growth velocity is slow
- For members ≥ 2.5 years of age at initiation of treatment:
  - Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean
  - Pretreatment 1-year height velocity is > 2 SD below the mean
- Epiphyses are open

#### **E. Prader-Willi Syndrome**

Authorization of 6 months may be granted to members with Prader-Willi syndrome when the diagnosis was confirmed by genetic testing demonstrating ANY of the following:

- Deletion in the chromosomal 15q11.2-q13 region
- Maternal uniparental disomy in chromosome 15
- Imprinting defects, translocations, or inversions involving chromosome 15

#### **F. Noonan Syndrome**

Authorization of 6 months may be granted to members with Noonan syndrome when BOTH of the following criteria are met:

- Member has EITHER of the following:
  - Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean
  - Pretreatment 1-year height velocity is > 2 SD below the mean
- Epiphyses are open

#### **G. Short Stature Homeobox-Containing Gene (SHOX) Deficiency**

Authorization of 6 months may be granted to members with short stature homeobox-containing gene (SHOX) deficiency when ALL the following criteria are met:

- Diagnosis of SHOX deficiency was confirmed by molecular or genetic analyses
- Member has EITHER of the following:
  - Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean
  - Pretreatment 1-year height velocity is > 2 SD below the mean
- Epiphyses are open

#### **H. Adult Growth Hormone (GH) Deficiency**

Authorization of 6 months may be granted to members with adult growth hormone (GH) deficiency when ANY of the following criteria is met:

- Member meets BOTH of the following criteria:



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- Member has had 2 pretreatment pharmacologic provocative GH tests and both results demonstrated deficient GH responses defined as ANY of the following:
  - Insulin tolerance test (ITT) with a peak GH level  $\leq 5$  ng/mL
  - Macrilen with a peak GH level of  $< 2.8$  ng/mL
  - Glucagon stimulation test with a peak GH level  $\leq 3.0$  ng/mL in patients with a body mass index (BMI)  $\leq 30$  kg/m<sup>2</sup> and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI  $< 25$  kg/m<sup>2</sup>
  - Glucagon stimulation test with a peak GH level  $\leq 1.0$  ng/mL in patients with a BMI of  $\geq 25$  kg/m<sup>2</sup> and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI  $> 30$  kg/m<sup>2</sup>
- Member has a pretreatment IGF-1 level 0 to 2 SD below the mean for age and gender
- Member meets BOTH of the following criteria:
  - Member has had 1 pretreatment pharmacologic provocative GH test that demonstrated deficient GH responses defined as any of the following:
    - Insulin tolerance test (ITT) with a peak GH level  $\leq 5$  ng/mL
    - Macrilen with a peak GH level of  $< 2.8$  ng/mL
    - Glucagon stimulation test with a peak GH level  $\leq 3.0$  ng/mL in patients with a body mass index (BMI)  $\leq 30$  kg/m<sup>2</sup> and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI  $< 25$  kg/m<sup>2</sup>
    - Glucagon stimulation test with a peak GH level  $\leq 1.0$  ng/mL in patients with a BMI of  $\geq 25$  kg/m<sup>2</sup> and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI  $> 30$  kg/m<sup>2</sup>
  - Member has a pretreatment IGF-1 level  $> 2$  SD below the mean for age and gender
- Member meets BOTH of the following criteria:
  - Member has organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) with  $\geq 3$  documented pituitary hormone deficiencies (see Appendix B)
  - Member has a pretreatment IGF-1 level  $> 2$  SD below the mean for age and gender<sup>26</sup>
- Member has genetic or congenital structural hypothalamic-pituitary defects (see Appendix C)
- Member has childhood-onset GH deficiency and a congenital abnormality of the CNS, hypothalamus or pituitary (see Appendix C)

### III. CONTINUATION OF THERAPY

#### A. Pediatric Growth Hormone (GH) Deficiency, Turner Syndrome, Noonan Syndrome, Chronic Kidney Disease (CKD), Small Gestational Age (SGA), Short Stature



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### **Homeobox-Containing Gene (SHOX) Deficiency, Congenital Adrenal Hyperplasia, Cerebral Palsy, Cystic Fibrosis, or Russell-Silver Syndrome**

Authorization of 6 months may be granted for continuation of therapy for pediatric growth hormone (GH) deficiency, Turner syndrome, Noonan syndrome, chronic kidney disease (CKD), small gestational age (SGA), short stature homeobox-containing gene (SHOX) deficiency, congenital adrenal hyperplasia, cerebral palsy, cystic fibrosis, or Russell-Silver syndrome when ALL of the following criteria are met:

- Member is currently receiving the requested medication or another growth hormone product (e.g., Norditropin) indicated for pediatric GH deficiency, Turner syndrome, Noonan syndrome, CKD, SGA, SHOX deficiency, congenital adrenal hyperplasia, cerebral palsy, cystic fibrosis, or Russell-Silver Syndrome
- Epiphyses are open (confirmed by X-ray or X-ray is not available)
- Member's growth rate is > 2 cm/year<sup>16,17</sup> unless there is a documented clinical reason for lack of efficacy (e.g., on treatment less than 1 year, nearing final adult height/late stages of puberty)

### **B. Prader-Willi Syndrome**

Authorization of 6 months may be granted for continuation of therapy for Prader-Willi syndrome when BOTH of the following criteria is met:

- Member is currently receiving the requested medication or another growth hormone product (e.g., Norditropin) indicated for Prader-Willi syndrome
- Member's body composition and psychomotor function have improved or stabilized in response to GH therapy

### **C. Adult Growth Hormone (GH) Deficiency**

Authorization of 6 months may be granted for continuation of therapy for adult growth hormone (GH) deficiency when BOTH of the following criteria is met:

- Member is currently receiving the requested medication or another growth hormone product (e.g., Norditropin) indicated for adult GH deficiency
- Member meets ANY of the following criteria:
  - Current IGF-1 level is not elevated for age and gender
  - Member has organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) with ≥ 3 documented pituitary hormone deficiencies (see Appendix B)
  - Member has genetic or congenital structural hypothalamic-pituitary defects (see Appendix C)<sup>26</sup>
  - Member has childhood-onset GH deficiency and a congenital abnormality of the CNS, hypothalamus, or pituitary (see Appendix C)

## **IV. APPENDICES**

### **A. Appendix A: Examples of Hypothalamic/Pituitary/CNS Disorders**



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1. Congenital genetic abnormalities
  - a. Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)
  - b. Growth hormone releasing hormone (GHRH) receptor gene defects
  - c. GH secretagogue receptor gene defects
  - d. GH gene defects
2. Congenital structural abnormalities
  - a. Optic nerve hypoplasia/septo-optic dysplasia
  - b. Agenesis of corpus callosum
  - c. Empty sella syndrome
  - d. Ectopic posterior pituitary
  - e. Pituitary aplasia/hypoplasia
  - f. Pituitary stalk defect
  - g. Holoprosencephaly
  - h. Encephalocele
  - i. Hydrocephalus
  - j. Anencephaly or prosencephaly
  - k. Arachnoid cyst
  - l. Other mid-line facial defects (e.g., single central incisor, cleft lip/palate)
  - m. Vascular malformations
3. Acquired structural abnormalities (or causes of hypothalamic/pituitary damage)
  - a. CNS tumors/neoplasms (e.g., craniopharyngioma, glioma/astrocytoma, pituitary adenoma, germinoma)
  - b. Cysts (Rathke cleft cyst or arachnoid cleft cyst)
  - c. Surgery
  - d. Radiation
  - e. Chemotherapy
  - f. CNS infections
  - g. CNS infarction
  - h. Inflammatory processes (e.g., autoimmune hypophysitis)
  - i. Infiltrative processes (e.g., sarcoidosis, histiocytosis, hemochromatosis)
  - j. Head trauma/traumatic brain injury
  - k. Aneurysmal subarachnoid hemorrhage
  - l. Perinatal or postnatal trauma
  - m. Surgery of the pituitary or hypothalamus

**B. Appendix B: Pituitary Hormones (Other than Growth Hormone)**

1. Adrenocorticotrophic hormone (ACTH)
2. Antidiuretic hormone (ADH)
3. Follicle stimulating hormone (FSH)
4. Luteinizing hormone (LH)
5. Thyroid stimulating hormone (TSH)





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## 6. Prolactin

### C. Appendix C: Requirements for GH-Stimulation Testing in Adults

1. Testing for adult GHD is not required
  - a. Three or more pituitary hormone deficiencies and low IGF-1
  - b. Congenital structural abnormalities
    - i. Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)
    - ii. GHRH receptor-gene defects
    - iii. GH-gene defects associated with brain structural defects
    - iv. Single central incisor
    - v. Cleft lip/palate
  - c. Acquired causes (i.e., perinatal insults)
2. Testing for adult GHD is required
  - a. Acquired
    - i. Skull-base lesions
    - ii. Pituitary adenoma
    - iii. Craniopharyngioma
    - iv. Rathke's cleft cyst
    - v. Meningioma
    - vi. Glioma/astrocytoma
    - vii. Neoplastic sellar and parasellar lesions
    - viii. Chordoma
    - ix. Hamartoma
    - x. Lymphoma
    - xi. Metastases
    - xii. Other brain injury
    - xiii. Traumatic brain injury
    - xiv. Sports-related head trauma
    - xv. Blast injury
    - xvi. Infiltrative/granulomatous disease
    - xvii. Langerhans cell histiocytosis
    - xviii. Autoimmune hypophysitis (primary or secondary)
    - xix. Sarcoidosis
    - xx. Tuberculosis
    - xxi. Amyloidosis
  - b. Surgery to the sella, suprasellar, and parasellar region
  - c. Cranial irradiation
  - d. Central nervous system infections (bacteria, viruses, fungi, parasites)
  - e. Infarction/hemorrhage (e.g., apoplexy, subarachnoid hemorrhage, ischemic stroke, snake bite)
  - f. Empty sella





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- g. Hydrocephalus
- h. Idiopathic

### Approval Duration and Quantity Restrictions:

Initial and Renewal Approval: 6 months

**Quantity Level Limit:** Reference Formulary for drug specific quantity level limits

### References:

1. Genotropin [package insert]. New York, NY: Pfizer Inc.; August 2024.
2. Humatrope [package insert]. Indianapolis, IN: Eli Lilly and Company; December 2023.
3. Norditropin [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; February 2018.
4. Nutropin AQ [package insert]. South San Francisco, CA: Genentech, Inc.; December 2016.
5. Omnitrope [package insert]. Princeton, NJ: Sandoz Inc.; November 2024.
6. Saizen [package insert]. Rockland, MA: EMD Serono Inc.; May 2018.
7. Zomacton [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; April 2024.
8. Congilio SJ, Stevenson RD, Rogol AD. Apparent growth hormone deficiency in children with cerebral palsy. *Dev Med Child Neurol*. 1996;38(9):797-804.
9. Shim ML, Moshang T, Oppenheim WL, et al. Is treatment with growth hormone effective in children with cerebral palsy? *Dev Med Child Neurol*. 2004;46(8):569-71.
10. Gallagher MP, Levine LS, Oberfield SE. A review of the effects of therapy on growth and bone mineralization in children with congenital adrenal hyperplasia. *Growth Horm IGF Res*. 2005;15 Suppl A:S26-30.
11. Lin-Su K, Vogiatzi MG, Marshall I, et al. Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2005;90:3318-3325.
12. Quintos JB, Vogiatzi MG, Harbison MD, et al. Growth hormone therapy alone or in combination with gonadotropin-releasing hormone analog therapy to improve the height deficit in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2001;86(4):1511-1517.
13. Thaker V, Carter B, Putman M. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. *Cochrane Database Syst Rev*. 2021;8(8):CD008901.
14. Wakeling EL et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. *Nat Rev Endocrinol*. 2017;13(2):105-124.
15. Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, genetics, and therapy of short stature in children: A Growth Hormone Research Society international perspective. *Horm Res Paediatr*. 2019;92(1):1-14.
16. Gharib H, Cook DM, Saenger PH, et al. American Association of Clinical Endocrinologists Growth Hormone Task Force. Medical guidelines for clinical practice for growth hormone use in adults and children 2003 Update. *Endocr Pract*. 2003;9(1):64-76.
17. National Institute for Clinical Excellence: Guidance on the use of human growth hormone (somatropin) for the treatment of growth failure in children. May 2010. <http://www.nice.org.uk/guidance/ta188>. Accessed January 20, 2025.



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18. Wilson TA, Rose SR, Cohen P, et al. Update of Guidelines for the Use of Growth Hormone in Children: The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr*. 2003;143:415-421.
19. Franklin SL, Geffner ME. Growth hormone: the expansion of available products and indications. *Pediatr Clin North Am*. 2011;58:1141-1165.
20. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86:361-397.
21. Deal CL, Tony M, Hoybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013;98:E1072-E1087.
22. Blum WF, Crowe BJ, Quigley CA, et al. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: two-year results of a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab*. 2007;92:219-228.
23. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab*. 2013;98(8):E1383-92.
24. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1587-1609.
25. Deal C, Hasselmann C, Pfaffle RW, et al. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. *Horm Res Paediatr*. 2013;79:283-292.
26. Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. *Endocr Pract*. 2019; 25: 1191-1232.
27. Butler MG, Miller JL, Forster JL. Prader-Willi syndrome – clinical genetics, diagnosis and treatment approaches: An update. *Curr Pediatr Rev*. 2019;15(4):207-244.